Pharmacovigilance Focus

Monitoring the safety of off-label medicine use

Medicine labels contain important information on the conditions of use. These conditions typically include the indication, dosage, frequency of administration, and route of administration. Other important conditions of use can include the age range of patients, duration of treatment, and contraindications to use of the medicine. Deviations from the conditions of use set forth in the label constitute off-label use.

In the USA, off-label use is legal. While the Food and Drug Administration (FDA) regulates the marketing of medicines, it does not regulate prescribing practices. In one study (1), approximately 21 per cent of drug use in office-based practice was for off-label use. Off-label use may occur for a variety of reasons. For example, there are some diseases for which no adequate, labelled treatment exists. In these situations, prescribers use medicines for off-label indications. In the case of medicines for children, many drugs have never been studied in children, so there has been extensive off-label use in children, although there are ongoing efforts to correct this situation. In some cases, there may be a reasonable body of published evidence to support off-label use. In other cases, such use is speculative. However, off-label use may become part of accepted practice, and may be part of professional society guidelines.

Because off-label use is common, there is a public health imperative to monitor the safety of medicines when used off-label. First and foremost, monitoring the safety of medicines in off-label settings is necessary to gain information on the usage of medicines in these settings. While formal study of medication safety would be optimal in these settings, such studies are often not available. Thus, safety monitoring plays a critical role. Data derived from monitoring safety in an off-label setting can also potentially be relevant to the safety of the medicine when used according to the label. In addition, data derived in the off-label setting may serve as a stimulus for more formal study.

There are many specific concerns that need to be addressed when monitoring the safety of medicines in an off-label setting. Many factors that could affect the safety of the medicine could be different in the off-label compared to the on-label setting. These factors include the age of patients, range of co-morbidities, use of concomitant medication, drug-disease interactions and differences in pharmacokinetics and pharmacodynamics.

Despite the importance of monitoring the safety of medicines in an off-label setting, there are many challenges that this situation presents. First, spontaneous reports do not always contain the indication for use or other details that would allow one to determine that the medicine was used in a manner not consistent with the product's label. Second, the identification of an adverse drug reaction in the off-label setting does not necessarily mean that this reaction is limited to that setting.

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Despite these limitations, spontaneous reports can be useful in determining adverse drug reactions when medicines are used off-label.

Drug utilization databases may be helpful in monitoring off-label use of medicines. Though such databases do not typically contain information on indications for use, they can be helpful in identifying other aspects of off-label use. For example, drug utilization data may shed light on the age range of patients using a medicine, the duration of therapy, concomitant medication used, and dosages prescribed. Review of such data may indicate that there is substantial off-label use and this may provide valuable information for safety monitoring purposes.

Drug use databases typically do not have any information on medical diagnoses, so they are not suitable for identifying adverse events. Nonetheless, they can be useful for identifying trends that may require further study. Administrative healthcare databases that contain information both on drug use data and medical diagnoses can also be useful for identifying trends in off-label use, though medical record review may be necessary to determine the indication for usage. Electronic medical records may be more useful than administrative healthcare databases if indication for use is linked to the drug prescribed. Finally, published clinical trials studying off-label use may be a valuable source of information on adverse drug reactions. However, the limitations of clinical trials for ascertaining adverse event information are well known.

One example of the importance of monitoring for adverse events in the off-label setting is seen with the drug tiagabine, whose labelled indication in the USA is for adjunctive therapy in adults and children over 12 years of age in the treatment of partial seizures. Post-marketing reports indicated that this medicine was being used by persons without epilepsy, and that these persons experienced seizures after tiagabine was started. The product's label was updated to include this information.

In summary, the off-label use of medicines is common. Monitoring of adverse events in this setting is important, though there are many challenges in doing so.

Reference: Radley et al. *Arch Intern Med* 2006; **166**:1021-1026.

Drotrecogin alfa: what relation to thrombosis?

Drotrecogin alfa (activated) is a recombinant form of human activated protein C that has antithrombotic, anti-inflammatory and profibrinolytic activities. It is used mainly in intensive care as a treatment for severe sepsis (sepsis associated with acute organ dysfunction). It is administered in multiple slow infusions, as a rule, at a dose of 24 μg/kg/hour for four days (1).

Sepsis is a complex illness involving both infection and inflammation when the body's response is systemic, instead of being localized to the site of infection. This "overreaction" to the infection may result in organ damage and is more dangerous than the initial infection itself (2).

Patients who die during episodes of sepsis are more likely to have coagulation defects, including lower levels of circulating antithrombin III and protein C. The latter is a vitamin K-dependent anticoagulant protease. In sepsis, protein C deficiency appears before the onset of observable indicators of septic shock.

The administration of an exogenous analogue may modulate the patient's

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response during sepsis (1, 3). The only serious adverse reaction observed in clinical trials to drotrecogin alfa was bleeding (3, 4).

Description of new ADR reports

Thirteen non-duplicate reports of thrombotic events in septic patients treated with drotrecogin alfa were reported to VigiBase, the database of the WHO Collaborating Centre for International Drug Monitoring, in the period 2002 to 2007. There were 12 reports from the USA and one from the United Kingdom. The reports are summarized below.

1. A General Practitioner (GP) described a 66-year-old male who developed thrombosis after administration of drotrecogin alfa. No details were reported.

2. A 72-year-old male was treated with drotrecogin alfa for three days. On the second day of treatment, pulmonary haemorrhage and thrombosis were observed.

3. A 34-year-old male was treated with drotrecogin alfa for six days in 2002. Concomitant medication comprised antibiotics as well as paracetamol and hydrocodone bitartrate. The report, sent by a GP, specified thrombosis, multiple organ failure and gangrene as adverse effects. Onset appeared eight days after termination of treatment.

4. A 66-year-old male was treated with drotrecogin alfa for three days. Concomitant medication comprised paracetamol, codeine, atenolol, lorazepam, triamcinolone, propofol, dopamine, levofloxacin, morphine, famotidine, salbutamol, metoclopramide, diazepam, midazolam, thiamine, piperacillin-tazobactam combination and heparin. The dosage and other treatment data were missing. Adverse reactions observed on the last day of drotrecogin treatment were deep venous thrombophlebitis and thrombosis.

5. A pharmacist described a 45-year-old female who was administered drotrecogin alfa for four days. Concomitant medication comprised dopamine and norepinephrine. Adverse effects described were intestinal ischaemia, decreased prothrombin level and thrombosis.

6. A pharmacist described a 72-year-old male treated with drotrecogin alfa for four days. Concomitant medication comprised sodium bicarbonate, pantoprazole, norepinephrine, vasopressin, paracetamol, dopamine, amiodarone, vancomycin and piperacillin-tazobactam combination. Adverse reactions described were anaemia, discoloured faeces and thrombosis.

7. A 68-year-old male was administered drotrecogin alfa for five days. Concomitant medication comprised cefotaxime, clarithromycin, amiodarone for two days, hydrocortisone for eight days and lorazepam for two days. One day after termination of drotrecogin treatment the patient developed thrombosis.

8. A pharmacist described an 86-year-old male who was treated with drotrecogin alfa for two days. No concomitant medication was reported. Life-threatening adverse reactions comprised hypotension, gastrointestinal haemorrhage and thrombosis. Positive dechallenge was also observed.

9. A physician reported the case of a female treated with drotrecogin alfa who developed thrombosis. No details were disclosed.

10. A pharmacist described a 63-year-old female treated with drotrecogin alfa for three days. Concomitant medication comprised ranitidine, azithromycin, ceftriaxone, dopamine and norepinephrine. Adverse reactions reported were

increased blood chloride and urea, hypernatraemia, hypokalaemia, hyperglycaemia, peripheral oedema, thrombocythaemia and thrombosis. Dechallenge appeared to be negative. No further information was provided.

11. A physician described a 70-year-old female treated with drotrecogin alfa for two days. Reported adverse effects were rash, jaundice, rectal disorders, bacterial infection, peritonitis and thrombosis.

12. A health professional reported the case of a 29-year-old female treated with drotrecogin alfa for two days. Concomitant medication comprised norepinephrine and dobutamine. Adverse reactions were haemorrhage and thrombosis.

13. A physician reported a 30-year-old female who was administered drotrecogin alfa (no other information was available). The adverse reaction was thrombosis.

Evaluation of reports

Six of the thirteen reports do not mention concomitant medication. Because of the clinical situation in which drotrecogin is used, it is almost certain that other medicines were co-administered. Thus, it is possible that some concomitantly used but undisclosed medicine might have contributed to the adverse effect.

Seven reports (3, 4, 5, 6, 7, 10 and 12) describe a range of concomitant medications. According to European Union Summaries of Product Characteristics (SPCs) as well as an international database (5) of these medicines, only propofol (administered in a single case) has the recognized, although very rare, adverse effect of thrombophlebitis (6).

Signal assessment

On the basis of pharmacological properties of drotrecogin alfa, administration is unlikely to lead to thrombosis. On the contrary, drotrecogin use is frequently associated with bleeding, related to its antithrombotic and profibrinolytic properties (1). In a Phase III placebo controlled clinical trial, the incidence of thrombotic events was similar in the drotrecogin and placebo arms (4). This was confirmed by analysis of results from combined clinical trials. When compared with placebo, patients in the active treatment arms experienced numerically fewer thrombotic events, although the difference was not statistically significant (7).

Thrombosis frequently occurs in patients with severe sepsis (7). Disseminated intravascular coagulation (DIC) may develop in 30-50% of patients with severe sepsis and septic shock, especially when caused by Gram negative bacteria. The mortality of sepsis is correlated with the development and severity of DIC (8). Protein C serves as an important anticoagulant compensatory mechanism. The cytokines produced in sepsis incapacitate the protein C pathway. One of the critical mediators of DIC is the release of a transmembrane glycoprotein tissue factor. This is released in response to exposure to cytokines or endotoxin and plays a major role in the development of DIC in septic conditions. For this reason, drotrecogin alfa is recommended in the therapy of DIC (8, 9). Additionally, a retrospective subgroup analysis of a clinical trial demonstrated a lower mortality rate among patients treated with drotrecogin alfa who met the criteria for DIC (10).

Hence, the conclusion is that in these spontaneous reports a manifestation of the underlying disease was reported as a possible adverse drug reaction. This hypothesis is further supported by the following.

- Clinical manifestation of DIC is extremely variable (9). The pathological processes involved deplete the body of its platelets and coagulation factors and

so, paradoxically, may lead to both thrombus formation and haemorrhage.

- Septic patients are generally treated in intensive care units but the adverse effect reporters (if disclosed) were mostly GPs, pharmacists and other health professionals, possibly not possessing detailed information.

- On consulting the WHO database, it can be seen that other reports on drotrecogin alfa between 2002 and 2007 specified various haemorrhages (the well-known adverse effects of drotrecogin alfa), as well as 43 reports of DIC itself.

Conclusion

In 13 reports of thrombosis associated with the use of drotrecogin alfa, retrieved from VigiBase, it appears likely that the reported thrombotic events represent a manifestation of the underlying disease process (severe sepsis), rather than an adverse reaction to any administered medicine. This analysis underlines the importance of considered assessment of all reported adverse drug reactions data.

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Epidemiology and Prevention of Vaccine-Preventable Diseases

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On the cover

"Die Spanische Krankheit" ("The Spanish Flu") ink drawing by Alfred Kubin, circa 1920. Kubin (1877-1959) studied in Munich and was associated with German expressionism. He was a contemporary of Edvard Munch, who also recorded his experience with the 1918 influenza pandemic. This work illustrates the figure of Death and the victims of the influenza pandemic in a way similar to that used in European woodcuts to depict the bubonic plague centuries earlier. The drawing is in a private collection.

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Milestones in the History of Vaccination

400BCE Hippocrates describes diphtheria, epidemic jaundice, and other conditions

1100s Variolation for smallpox first reported in China

1721 Variolation introduced into Great Britain

1796 Edward Jenner inoculates James Phipps with cowpox, and calls the procedure vaccination ("vacca" is Latin for cow)

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Milestones in the History of Vaccination

1870 Louis Pasteur creates the first live attenuated bacterial vaccine (chicken cholera)

1884 Pasteur creates the first live attenuated viral vaccine (rabies)

1885 Pasteur first uses rabies vaccine in a human

1887 Institut Pasteur established

1900 Paul Ehrlich formulates receptor theory of immunity

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Milestones in the History of Vaccination

1901 First Nobel Prize in Medicine to von Behring for diphtheria antitoxin

1909 Theobald Smith discovers a method for inactivating diphtheria toxin

1919 Calmette and Guerin create BCG, the first live attenuated bacterial vaccine for humans

1923 First whole-cell pertussis vaccine tested
Gaston Ramon develops diphtheria toxoid

1926 Ramon and Christian Zoeller develop tetanus toxoid

Milestones in the History of Vaccination

1927 Yellow fever virus isolated

1931 Goodpasture describes a technique for viral culture in hens' eggs

1936 Thomas Francis and Thomas Magill develop the first inactivated influenza vaccine

1948 John Enders and colleagues isolate Lansing Type II poliovirus in human cell line

1954 Enders and Peebles isolate measles virus
Francis Field Trial of inactivated polio vaccine

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Milestones in the History of Vaccination

1955	1961	1963	1965	1966
Inactivated polio vaccine licensed	Human diploid cell line developed	Measles vaccine licensed Trivalent oral polio vaccine licensed	Bifurcated needle for smallpox vaccine licensed	World Health Assembly calls for global smallpox eradication

Milestones in the History of Vaccination

1967 Maurice Hilleman develops Jeryl Lynn strain of mumps virus

1969 Stanley Plotkin develops RA27/3 strain of rubella vaccine virus

1971 MMR vaccine licensed

1977 Last indigenous case of smallpox (Somalia)

1979 Last wild poliovirus transmission in the U.S.

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Milestones in the History of Vaccination

1981 First hepatitis B vaccine licensed

1983 Smallpox vaccine withdrawn from civilian market

1986 First recombinant vaccine licensed (hepatitis B)
National Childhood Vaccine Injury Act

1989 Two-dose measles vaccine recommendation

1990 First polysaccharide conjugate vaccine licensed (*Haemophilus influenzae* type b)

Milestones in the History of Vaccination

1994
Polio elimination certified in the Americas
Vaccines for Children program begins

1995
Varicella vaccine licensed
Hepatitis A vaccine licensed
First harmonized childhood immunization schedule published

1996
Acellular pertussis vaccine licensed for infants

1997
Sequential polio vaccination recommended

1998
First rotavirus vaccine licensed

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APPENDICES

A Schedules and Recommendations

B Vaccines

C Vaccine Storage and Handling

D Vaccine Administration

1999
Exclusive use of inactivated polio vaccine recommended
Rotavirus vaccine withdrawn

2000
Pneumococcal conjugate vaccine licensed for infants

2003
Live attenuated influenza vaccine licensed

2004
Inactivated influenza vaccine recommended for all children 6–23 months of age

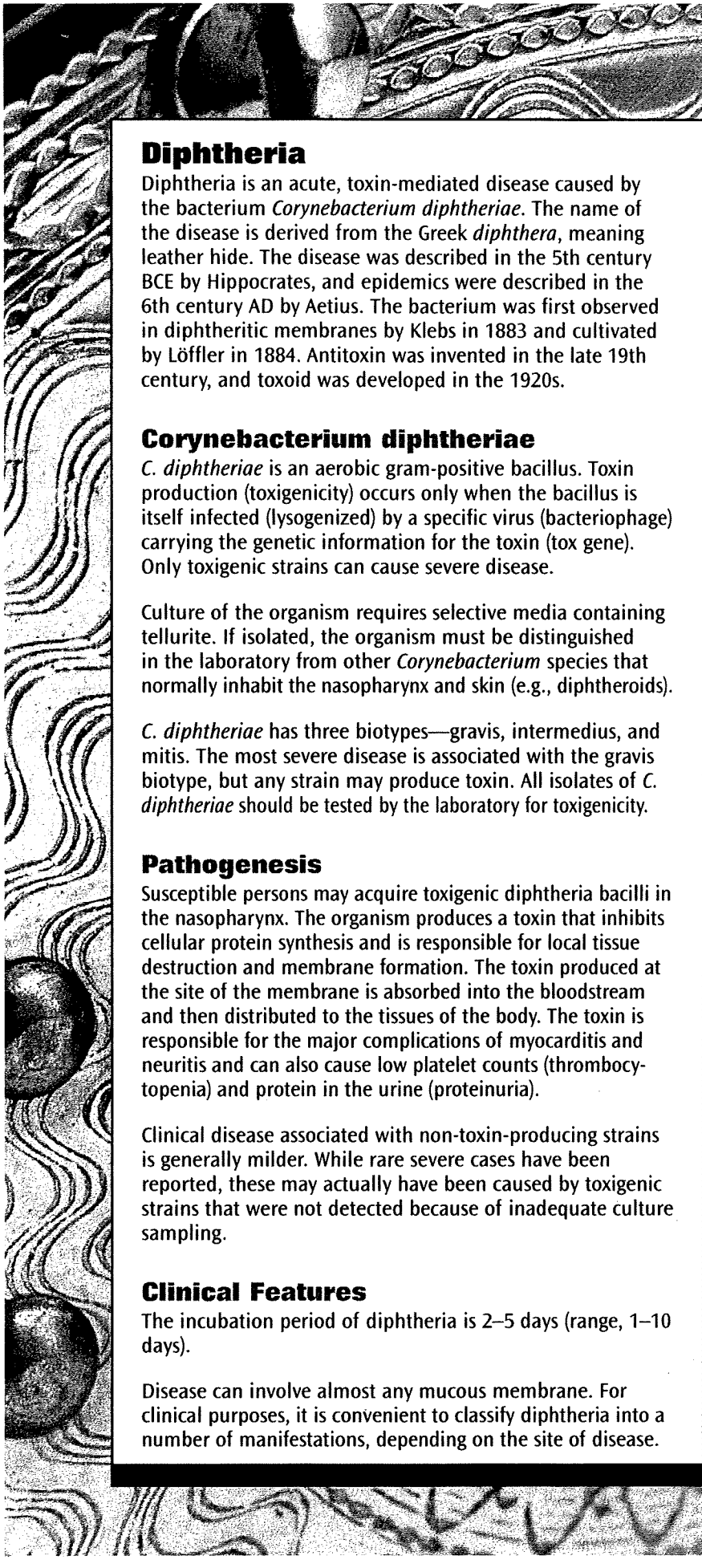
2004
Indigenous transmission of rubella virus interrupted

Milestones in the History of Vaccination

2005	2005	2006	2006	2006
Acellular pertussis vaccines licensed for adolescents and adults	MMR-varicella (MMRV) licensed	Second generation rotavirus vaccine licensed	First human papillomavirus vaccine licensed	First herpes zoster vaccine licensed

Vaccines and Related Products Distributed in the United States

Vaccine/Biologic	Brand Name	Manufacturer	Type	How Supplied
Diphtheria, Tetanus, acellular Pertussis	Infanrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Diphtheria, Tetanus, acellular Pertussis	Tripedia®	sanofi-pasteur	Inactivated	single-dose vial
Diphtheria, Tetanus, acellular Pertussis	Daptacel®	sanofi-pasteur	Inactivated	single-dose vial
Diphtheria, Tetanus, acellular Pertussis + Hib	TriHIBit®	sanofi-pasteur	Inactivated	single-dose vial
Diphtheria, Tetanus, acellular Pertussis +Hep B + IPV	Pediarix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Diphtheria, Tetanus, acellular Pertussis + Hib + IPV	Pentacel®	sanofi-pasteur	Inactivated	single-dose vial
Diphtheria, Tetanus, acellular Pertussis + IPV	Kinrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Diphtheria, Tetanus (DT; ped <7yrs, P-free)	generic	sanofi-pasteur	Inactivated	single-dose vial
Tetanus, diphtheria, adsorbed (Td; >7yrs, P-free)	Decavac®	sanofi-pasteur	Inactivated	single-dose syringe
Tetanus, diphtheria, adsorbed (Td; >7yrs)	generic	Mass Biologic Labs	Inactivated	15-dose vial
Tetanus, diphtheria, acellular Pertussis (Tdap; 10-64 yrs)	Boostrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Tetanus, diphtheria, acellular Pertussis (Tdap; 11-64 yrs)	Adacel™	sanofi-pasteur	Inactivated	single-dose vial
Tetanus toxoid (TT; >7 yrs) adsorbed	generic	sanofi-pasteur	Inactivated	10-dose vial
Tetanus toxoid (TT; adult booster use only)	generic	sanofi-pasteur	Inactivated	15-dose vial
Tetanus immune globulin (TIG)	HyperTET™	Talecris	Human immunoglobulin	single-dose syringe
Haemophilus influenzae type b (PRP-T)	ActHIB®	sanofi-pasteur	Inactivated	single-dose vial
Haemophilus influenzae type b (HbOC)	HibTITER®	Wyeth	Inactivated	single-dose vial
Haemophilus influenzae type b (PRP-OMP)	PedvaxHIB®	Merck	Inactivated	single-dose vial
Haemophilus influenzae type b (PRP-OMP) + Hep B	Comvax®	Merck	Inactivated	single-dose vial
Hepatitis A: ped/adol & adult formulations	Havrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Hepatitis A: ped/adol & adult formulations	Vaqta®	Merck	Inactivated	single-dose vial or syringe
Hepatitis A immune globulin	GamaSTAN™	Talecris	Human immunoglobulin	2 mL and 10 mL vials
Hepatitis B: ped/adol & adult formulations	Engerix-B®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Hepatitis B: ped/adol & adult formulations	Recombivax HB®	Merck	Inactivated	single-dose vial
Hepatitis B dialysis formulation	Recombivax HB®	Merck	Inactivated	single-dose vial
Hepatitis B immune globulin (HBIG)	HyperHEP B™	Talecris	Human immunoglobulin	1 mL syringe, 1 mL or 5 mL vial
Hepatitis B immune globulin (HBIG): ped formulation	HyperHEP B™	Talecris	Human immunoglobulin	single-dose 0.5 mL neonatal syringe
Hepatitis B immune globulin (HBIG)	Nabi-HB®	Nabi	Human immunoglobulin	single-dose vial
Hepatitis A & B: adult formulation	Twinrix®	GlaxoSmithKline	Inactivated	single-dose vial or syringe
Human papillomavirus (HPV)	Gardasil®	Merck	Inactivated	single-dose vial or syringe
Influenza (trivalent inactivated influenza vaccine [TIV])	Fluarix®	GlaxoSmithKline	Inactivated	10 single-dose syringes
Influenza (live attenuated influenza vaccine [LAIV])	FluMist®	Medimmune	Live, intranasal	10 single-use sprayers
Influenza (TIV)	Afluria®	CSL Biotherapies	Inactivated	single-dose syringe & 10-dose vial
Influenza (TIV)	Fluvirin®	Novartis	Inactivated	single-dose syringe & 10-dose vial
Influenza (TIV)	Fluzone®	sanofi-pasteur	Inactivated	10-dose vial
Influenza (TIV; >36 mos; no preservative)	Fluzone®	sanofi-pasteur	Inactivated	single-dose syringe (0.5 mL)
Influenza (TIV; ped 6-35 mos; no preservative)	Fluzone®	sanofi-pasteur	Inactivated	single-dose syringe (0.25 mL)
Influenza (TIV; >18 yrs)	FluLaval™	GlaxoSmithKline	Inactivated	10-dose vial
Measles, Mumps, Rubella (MMR)	M-M-R II®	Merck	Live, attenuated	single-dose vial
Measles, Mumps, Rubella + Varicella (MMRV)	ProQuad®	Merck	Live, attenuated	single-dose vial
Meningococcal conjugate (A/C/Y/W-135)	Menactra®	sanofi pasteur	Inactivated	single-dose vial
Meningococcal polysaccharide (A/C/Y/W-135)	Menomune®	sanofi pasteur	Inactivated	single-dose vial
Pneumococcal conjugate, 7-valent	Prevnar®	Wyeth	Inactivated	single-dose vial
Pneumococcal polysaccharide, 23-valent	Pneumovax 23®	Merck	Inactivated	single-dose vial or 5-dose vial
Polio (IPV)	IPOL®	sanofi pasteur	Inactivated	single-dose syringe or 10-dose vial
Rotavirus	RotaTeq®	Merck	Live, oral	single-dose tube
Rotavirus	Rotarix®	GlaxoSmithKline	Live, oral	single-dose tube
Varicella	Varivax®	Merck	Live, attenuated	single-dose vial
Varicella Zoster Immune Globulin (VZIG) (IND)	VariZIG™	Cangene	Human Immunoglobulin	125-U vial
Zoster	Zostavax®	Merck	Live, attenuated	single-dose vial
Anthrax, adsorbed	BioThrax™	BioPort	Inactivated	multi-dose vial
Japanese encephalitis	JE-VAX®	sanofi pasteur	Inactivated	single-dose vial
Rabies	Imovax®	sanofi pasteur	Inactivated	single-dose vial
Rabies	RabAvert®	Novartis	Inactivated	single-dose vial
Rabies Immune Globulin (RIG)	Imogam Rabies-HT®	sanofi-pasteur	Human immunoglobulin	2 mL and 10 mL vials
Rabies Immune Globulin (RIG)	HyperRAB™	Talecris	Human immunoglobulin	2 mL and 10 mL vials
Typhoid VI polysaccharide	Typhim Vi®	sanofi-pasteur	Inactivated	single-dose syringe and 20-dose vial
Typhoid, live oral Ty21a	Vivotif®	Berna	Live, attenuated	4-capsule package
Yellow Fever	YF-Vax®	sanofi-pasteur	Live, attenuated	single- and 5-dose vial



Diphtheria

Diphtheria is an acute, toxin-mediated disease caused by the bacterium *Corynebacterium diphtheriae*. The name of the disease is derived from the Greek *diphthera*, meaning leather hide. The disease was described in the 5th century BCE by Hippocrates, and epidemics were described in the 6th century AD by Aetius. The bacterium was first observed in diphtheritic membranes by Klebs in 1883 and cultivated by Löffler in 1884. Antitoxin was invented in the late 19th century, and toxoid was developed in the 1920s.

Diphtheria

- Greek *diphthera* (leather hide)
- Recognized by Hippocrates in 5th century BCE
- Epidemics described in 6th century
- *C. diphtheriae* described by Klebs in 1883
- Toxoid developed in 1920s

Corynebacterium diphtheriae

C. diphtheriae is an aerobic gram-positive bacillus. Toxin production (toxigenicity) occurs only when the bacillus is itself infected (lysogenized) by a specific virus (bacteriophage) carrying the genetic information for the toxin (tox gene). Only toxigenic strains can cause severe disease.

Culture of the organism requires selective media containing tellurite. If isolated, the organism must be distinguished in the laboratory from other *Corynebacterium* species that normally inhabit the nasopharynx and skin (e.g., diphtheroids).

C. diphtheriae has three biotypes—gravis, intermedius, and mitis. The most severe disease is associated with the gravis biotype, but any strain may produce toxin. All isolates of *C. diphtheriae* should be tested by the laboratory for toxigenicity.

Corynebacterium diphtheriae

- Aerobic gram-positive bacillus
- Toxin production occurs only when *C. diphtheriae* infected by virus (phage) carrying tox gene
- If isolated, must be distinguished from normal diphtheroid

Pathogenesis

Susceptible persons may acquire toxigenic diphtheria bacilli in the nasopharynx. The organism produces a toxin that inhibits cellular protein synthesis and is responsible for local tissue destruction and membrane formation. The toxin produced at the site of the membrane is absorbed into the bloodstream and then distributed to the tissues of the body. The toxin is responsible for the major complications of myocarditis and neuritis and can also cause low platelet counts (thrombocytopenia) and protein in the urine (proteinuria).

Clinical disease associated with non-toxin-producing strains is generally milder. While rare severe cases have been reported, these may actually have been caused by toxigenic strains that were not detected because of inadequate culture sampling.

Clinical Features

The incubation period of diphtheria is 2–5 days (range, 1–10 days).

Disease can involve almost any mucous membrane. For clinical purposes, it is convenient to classify diphtheria into a number of manifestations, depending on the site of disease.

Diphtheria Clinical Features

- Incubation period 2-5 days (range, 1-10 days)
- May involve any mucous membrane
- Classified based on site of infection
  - –anterior nasal
  - –pharyngeal and tonsillar
  - –laryngeal
  - –cutaneous
  - –ocular
  - –genital

Diphtheria

5

Pharyngeal and Tonsillar Diphtheria

- Insidious onset of exudative pharyngitis
- Exudate spreads within 2-3 days and may form adherent membrane
- Membrane may cause respiratory obstruction
- Fever usually not high but patient appears toxic

Anterior Nasal Diphtheria

The onset of anterior nasal diphtheria is indistinguishable from that of the common cold and is usually characterized by a mucopurulent nasal discharge (containing both mucus and pus) which may become blood-tinged. A white membrane usually forms on the nasal septum. The disease is usually fairly mild because of apparent poor systemic absorption of toxin in this location, and it can be terminated rapidly by antitoxin and antibiotic therapy.

Pharyngeal and Tonsillar Diphtheria

The most common sites of diphtheria infection are the pharynx and the tonsils. Infection at these sites is usually associated with substantial systemic absorption of toxin. The onset of pharyngitis is insidious. Early symptoms include malaise, sore throat, anorexia, and low-grade fever. Within 2–3 days, a bluish-white membrane forms and extends, varying in size from covering a small patch on the tonsils to covering most of the soft palate. Often by the time a physician is contacted, the membrane is greyish-green, or black if bleeding has occurred. There is a minimal amount of mucosal erythema surrounding the membrane. The membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding. Extensive membrane formation may result in respiratory obstruction.

The patient may recover at this point; or if enough toxin is absorbed, develop severe prostration, striking pallor, rapid pulse, stupor, and coma, and may even die within 6 to 10 days. Fever is usually not high, even though the patient may appear quite toxic. Patients with severe disease may develop marked edema of the submandibular areas and the anterior neck along with lymphadenopathy, giving a characteristic "bullneck" appearance.

Laryngeal Diphtheria

Laryngeal diphtheria can be either an extension of the pharyngeal form or can only involve this site. Symptoms include fever, hoarseness, and a barking cough. The membrane can lead to airway obstruction, coma, and death.

Cutaneous (Skin) Diphtheria

In the United States, cutaneous diphtheria has been most often associated with homeless persons. Skin infections are quite common in the tropics and are probably responsible for the high levels of natural immunity found in these populations. Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and membrane, but any chronic skin lesion may harbor *C diphtheriae* along with other organisms. Generally, the organisms isolated

from recent cases in the United States were nontoxigenic. The severity of the skin disease with toxigenic strains appears to be less than in other forms of infection with toxigenic strains. Skin diseases associated with nontoxigenic strains are no longer reported to the National Notifiable Diseases Surveillance System in the United States.

Other sites of involvement include the mucous membranes of the conjunctiva and vulvovaginal area, as well as the external auditory canal.

Complications

Most complications of diphtheria, including death, are attributable to effects of the toxin. The severity of the disease and complications are generally related to the extent of local disease. The toxin, when absorbed, affects organs and tissues distant from the site of invasion. The most frequent complications of diphtheria are myocarditis and neuritis.

Diphtheria Complications

- Most attributable to toxin
- Severity generally related to extent of local disease
- Most common complications are myocarditis and neuritis
- Death occurs in 5%-10%

Myocarditis may present as abnormal cardiac rhythms and can occur early in the course of the illness or weeks later, and can lead to heart failure. If myocarditis occurs early, it is often fatal.

Neuritis most often affects motor nerves and usually resolves completely. Paralysis of the soft palate is most frequent during the third week of illness. Paralysis of eye muscles, limbs, and diaphragm can occur after the fifth week. Secondary pneumonia and respiratory failure may result from diaphragmatic paralysis.

Other complications include otitis media and respiratory insufficiency due to airway obstruction, especially in infants.

Death

The overall case-fatality rate for diphtheria is 5%–10%, with higher death rates (up to 20%) among persons younger than 5 and older than 40 years of age. The case-fatality rate for diphtheria has changed very little during the last 50 years.

Laboratory Diagnosis

Diagnosis of diphtheria is usually made on the basis of clinical presentation since it is imperative to begin presumptive therapy quickly.

Culture of the lesion is done to confirm the diagnosis. It is critical to take a swab of the pharyngeal area, especially any discolored areas, ulcerations, and tonsillar crypts. Culture medium containing tellurite is preferred because it provides a selective advantage for the growth of this organism.